Introduction

Coumarins (1; bezopyran-2-ones) constitute an important subclass of naturally occurring flavonoids. These compounds occupy an important position in heterocyclic compounds because of their vast applications in pharmaceuticals industry. These have been used as anthelmintics\(^1\), hypnotics\(^2\), anti-HIV agents\(^3\)\(^4\). Coumarins have also been used as insecticides\(^5\), optical brighteners\(^6\) and dispersed fluorescent and laser dyes\(^7\)\(^8\).

\[\text{(1)}\]

3-Phenylcoumarins (2) constitute a small but important group of naturally occurring coumarins because of their diverse medicinal and photochemical utility. For many years only two naturally occurring 3-phenylcoumarins namely pachyrrhizin (3) and neofolin (4) were known but now many others have also been isolated from the natural source.

\[\text{(2)}\] \[\text{(3)}\]

7,2'-Dihydroxy-4'-methoxy-3-phenylcoumarin (5) and 7,2'-dihydroxy-4',5'-methylenedioxy-3-phenylcoumarin (6) have been isolated from the heart wood of *Dalbergia Oliveri*\(^9\) and glycyrin (7) from the roots of *Glycyrrhiza Spp*\(^10\).
Indicanine A (8; 4-hydroxy-5-methoxy-3-(4'-methoxyphenyl)-2''-(1-methylethenyl)-dihydrofurano[4'',5'':6,7]coumarin) has been isolated from the root bark of african medicinal plant *Erythrina Indica*\(^{11}\).

El-Seedi\(^{12}\) isolated 3-phenylcoumarin glucoside, asphodelin A (9; 3-(2'-hydroxy-p-O-\(\beta\)-D-glucopyranosyloxyphenyl)-4,7-dihydroxycoumarin from *Asphodelus Microcrus*.
Both synthetic and naturally occurring 3-phenylcoumarins possess diverse medicinal and photochemical utility some of which are briefly described below.

Arnoldi et al.\textsuperscript{13} synthesized variously substituted 3-phenylcoumarins (10) and found these compounds to show fungicidal activity both \textit{in vitro} and \textit{in vivo} against different phytopathogenic fungi.

\begin{center}
\begin{tikzpicture}
  \begin{scope}[scale=0.5]
    \draw (0,0) -- (0,2) -- (2,2) -- (2,0) -- cycle;
    \draw (4,0) -- (4,2) -- (6,2) -- (6,0) -- cycle;
    \draw (2,1) -- (4,1);
    \draw (2,1.5) -- (4,1.5);
    \node at (1,1) {$R^4$};
  \end{scope}
\end{tikzpicture}
\end{center}

Indicanine A (8; a naturally occurring coumarin) has been found to possess antimicrobial activity against \textit{S. aureus} and \textit{M. smegmatis}\textsuperscript{11}.

Kirkiracharian et al.\textsuperscript{14} synthesized variously substituted 4-hydroxy-3-phenylcoumarins (11) and found these compounds to exhibit HIV-1 protease inhibitory activity.

\begin{center}
\begin{tikzpicture}
  \begin{scope}[scale=0.5]
    \draw (0,0) -- (0,2) -- (2,2) -- (2,0) -- cycle;
    \draw (4,0) -- (4,2) -- (6,2) -- (6,0) -- cycle;
    \draw (2,1) -- (4,1);
    \draw (2,1.5) -- (4,1.5);
    \node at (1,1) {$R^1$};
  \end{scope}
\end{tikzpicture}
\end{center}
Chen et al.\textsuperscript{15} found 4-benzyl-3-(4'-chlorophenyl)-7-methoxycoumarin (12) to act as a potent competitive inhibitor of aromatase with respect to androgen substrate and significantly more potent than several known aromatase inhibitors such as letrozole (13), anastrozole (14), exemestane (15) etc.

\[
\text{MeO}
\]

(12) \hspace{1cm} (13)

Kawase et al.\textsuperscript{16} synthesized variously substituted 3-phenylcoumarins (16) and found these compounds to exhibit tumor specific cytotoxicity and multidrug resistance reversal activity.
El-Seedi\textsuperscript{12} found 3-phenylcoumarin glucoside, asphodelin A (9; 3-(2'-hydroxy-p-O-β-D-glucopyranosyloxyphenyl)-4,7-dihydroxy-coumarin) to exhibit antimicrobial activity.

Kabeya et al.\textsuperscript{17} synthesized hydroxylated 3-phenylcoumarins (17) found these compounds to exhibit horseradish peroxidase activity and free radical scavenger activity. Fais et al.\textsuperscript{18} synthesized variously substituted 3-phenylcoumarins (18) and found these compounds to exhibit potential tyrosinase inhibitory activity.

Matos et al.\textsuperscript{19} synthesized variously substituted 3-phenylcoumarins (19) and found these compounds to exhibit high selectivity to monoamine oxidase B enzyme.
Quezada et al.\textsuperscript{20} synthesized differently substituted 3-phenylcoumarins (20) and found these compounds to show vasorelaxant activity and platelet aggregatory activity up to thirty times than that shown by trans-resveratol (21).

Sashidhara et al.\textsuperscript{21} synthesized variously substituted 3-phenylcoumarins (22) and reported these compounds to act as antidepressant agents.
Recently Yang et al. synthesized variously substituted 3-phenylcoumarins (23) and found these compounds to act as potent antioxidants and antiproliferative agents.

\[
\begin{aligned}
\text{(23)} \\
\text{R}_8 \\
\end{aligned}
\]

Foote et al. synthesized a polymer from substituted triazine and substituted 3-phenylcoumarin (24) and found this polymer to act as an optical brightener.

\[
\begin{aligned}
\text{(24)} \\
\end{aligned}
\]

3-Phenylcoumarins have also been shown to play a vital role in electrophotographic and electroluminescent devices.

Cakir et al. synthesized some 3-phenylcoumarin substituted crown ethers (25) and studied equilibria on complexation with ion-pair interaction of sodium and potassium dyes viz. 4-(2-pyridylazo)resorcinol monosodium salt monohydrate (SPAR), Sodium picrate (SP) and potassium picrate (PP) and concluded that SPAR is more closely associated with crown compounds and is the best extracted organic sodium dye.
Synthesis of 3-phenylcoumarins

Amongst various methods known for the synthesis of 3-phenylcoumarins in literature, Perkin’s method is the first and most practically used method, which involves the condensation of phenylacetic acid with appropriate 2-hydroxybenzaldehyde in acetic anhydride. This method has been modified by several workers by varying the reaction conditions to get better yields brief description of which is given below.

Perkin-Oglialoro reaction

Perkin condensation\textsuperscript{28} modified by Oglialoro\textsuperscript{29} involves the condensation of 2-hydroxy benzaldehydes with a mixture of phenylacetic acid and acetic anhydride or sodium phenyl acetate with acetic anhydride (scheme 1). But this method has a limitation of using excess of acetic anhydride, elevated temperature, longer reaction time, tedious work up and unsatisfactory low yields.

Norland and Singer\textsuperscript{30} modified the Perkin reaction by heating 2-hydroxybenzaldehyde with phenylacetic acid and phenylacetic anhydride in presence of triethylamine to give 3-phenylcoumarin (scheme 2).
In another important modification by Rao and Srimannarayana\textsuperscript{31} 2-hydroxybenzaldehydes or 2-hydroxyacetophenones were refluxed with phenylacetyl chloride in acetone medium in the presence of anhydrous potassium carbonate to give 3-phenylcoumarin in good yield (70-90\%) but it required large reaction period of 30 hours (scheme 3).

Later Awasthi and Tiwari\textsuperscript{32} used N,N-dimethyl dichlorophosphoryloxomethylene ammonium chloride for the activation of phenylacetic acid before its reaction with 2-hydroxybenzaldehyde to provide 3-phenylcoumarin in 75-95\% yield (scheme 4).

![Scheme 4.](image)
Mohanti et al.\textsuperscript{33} modified Perkin reaction using phase transfer catalysis which involved reaction of 2-hydroxybenzaldehydes with phenylacetic anhydride in benzene-aqueous potassium carbonate biphase medium to get 3-phenyl coumarin in better yields (scheme 5).

Recently, Kumar and Makrandi\textsuperscript{34} reported the synthesis of 3-phenylcoumarins by reacting 2-hydroxybenzaldehydes with phenylacetic anhydride in activated barium hydroxide in dimethyl sulphoxide medium using microwave irradiations in very good yields in a single step (scheme 6).

Recently Taksande et al.\textsuperscript{35} reported the synthesis of 3-phenylcoumarins by a two step procedure. The phenylacetoxy ester obtained by condensation of 2-hydroxy benzaldehydes /2-hydroxyacetophenones with phenylacetic acid in presence of POCl\textsubscript{3} in pyridine medium on heating with potassium hydroxide in pyridine gave 3-phenylcoumarins (scheme 7).
Mashraqui et al.\textsuperscript{37} reported a single step synthesis of 3-phenylcoumarin using Mukaiyama esterification condition which involving reaction of salicylaldehyde and phenylacetic acid in presence of 2 mole equivalents of freshly crystallized 2-chloromethyl pyridinium iodide and triethylamine in dry acetonitrile under reflux in nitrogen atmosphere (scheme 8).
Other methods

By reduction of 4-hydroxy-3-phenylcoumarin

Ahluwalia and Mehta\textsuperscript{38} reported the synthesis of 3-phenylcoumarin from 4-hydroxy-3-phenylcoumarins, firstly tosylating 4-hydroxy group followed by reductive cleavage with zinc in presence of hydrochloric acid. Required 4-hydroxy-3-phenylcoumarins were obtained by the reaction of 2-hydroxyphenylbenzyl ketones with diethyl carbonate in presence of sodium methoxide (scheme 9).

![Scheme 9.](image)

By Wittig reaction

Narsimhan et al.\textsuperscript{39} synthesized 3-phenylcoumarin by heating ethyl \( \alpha \)-hydroxycinnamates which were obtained by reaction of 2-hydroxybenzaldehydes with ethoxycarbonyl phenylmethylene triphenylphosphoranes under Wittig reaction conditions (scheme 10).
Scheme 10.

From isoflavylum salts\textsuperscript{40}

Isoflavylium salts such as isoflavylum perchlorate on oxidation with chromium trioxide in presence of pyridine gave 3-phenylcoumarins (scheme 11).

Scheme 11.

From 2-methoxychalcones\textsuperscript{41}

Epoxides obtained by reaction of 2-methoxychalcone with hydrogen peroxide in alkanline medium on reaction with alcoholic sodium hydroxide rearranged into a hydroxycabxylic acid (2,3-(substitutedphenyl)-2-hydroxypropanoic acid) \textit{via} formation of \(\alpha\)-diketone which on heating with hydroiodic acid in acetic acid gave 3-phenylcoumarin (scheme 12).
Photochemical synthesis (From 3-bromocoumarin)\textsuperscript{42}

Meng et al. reported the synthesis of a 3-arylcoumarins from 3-bromocoumarin involving their photocoupling with aromatic compounds (scheme 13).

Using phenylacetic acid hydrazide

Nemeryuk et al.\textsuperscript{43} reported the synthesis of 3-arylcoumarins by reaction of 3-acyl and 3-ethoxycarbonyl coumarins with hydrazide of \textit{p}-nitrophenylacetic acid in presence of morpholine in ethanol medium at 18-20°C for 24 hours. (scheme 14).
Using arylacetonitrile

Mhiri et al.\textsuperscript{44} reported the synthesis of 3-phenylcoumarins by condensation of salicylaldehydes with various phenylacetonitriles catalyzed by anion exchange resin (scheme 15).

Scheme 14.

Scheme 15.
Present work

3-Phenyl coumarins, a sub-group of naturally occurring compounds with varied potential biological properties have been synthesized mainly by Perkin reaction involving condensation between 2-hydroxybenzaldehydes with phenylacetic acid or its derivatives. A Number of modifications in the reaction conditions have been reported in literature in order to get better yield of the compounds which have been discussed in previous pages, some of these involve the use of very hazardous solvents such as pyridine.

As in the previous chapter, the aroyloxy esters could easily be prepared by grinding phenols with aroyl chloride in presence of potassium carbonate in aqueous medium, it was thought worth to study the reaction of salicylaldehyde with phenylacetyl chloride or phenylacetic anhydride using grinding conditions which could yield 2-phenylacetoxybenzaldehyde or 3-phenylcoumarin.

Thus, a mixture of salicylaldehyde (5 mmol), phenylacetyl chloride (5 mmol), potassium carbonate (10 mmol) homogenized with 5 drops of water was ground in mortar with a pestle. The progress of the reaction was monitored by thin layer chromatography and salicylaldehyde was found to have reacted almost completely after 5 minutes. The reaction mixture was left at room temperature for 5 minutes for completion of reaction and acidified with conc. HCl after diluting it with ice cold water. The colourless solid thus obtained was crystallized from ethanol. In IR spectra it showed absorption at 1713 cm$^{-1}$ showing the presence of carbonyl group, characteristic of coumarin. In $^1$H NMR, it showed one proton signal at $\delta$ 7.80, characteristic of H-4 of coumarin along with peaks for other aromatic protons. Based on this data, compound was identified as 3-phenylcoumarin (27) which was further confirmed by comparison of m.p. (138-39°C) with literature value$^{30}$.

It appears that during the reaction, phenylacetox ester formed at the initial stage undergoes cyclisation immediately to give 3-phenylcoumarin directly in one step.

Above reaction was also carried out by using phenylacetic anhydride in place of phenylacetyl chloride, when similar results were obtained and 3-phenylcoumarin was obtained in almost similar yields.
The use of phenylacetyl chloride was thought to be superior over phenylacetic anhydride as acid chlorides are known to be more reactive than acid anhydrides. Secondly, phenylacetic anhydride has to be prepared from phenylacetic acid by reacting it with POCl$_3$ in pyridine or by reacting it with DCCI, an expensive chemical. Moreover, after the reaction with phenylacetic anhydride only half of the phenylacetic acid part is utilized and the other half goes waste.

Similarly, attempt was made to synthesize 4-methyl-3-phenylcoumarins and for this a mixture of 2-hydroxyacetophenone (5 mmol), phenylacetyl chloride (5 mmol), potassium carbonate (10 mmol) and 5 drops of water was ground in a mortar with a pestle. The progress of the reaction was monitored by TLC and after 5 minutes 2-hydroxy-5-methylacetophenone was found to have reacted almost completely and it was further left at room temperature for 5 minutes. The reaction mixture was acidified with conc. HCl after diluting with ice cold water. The colourless solid that separated out was filtered, washed with water and recrystallized from ethanol. Its IR showed absorption at 1713 cm$^{-1}$, due to carbonyl group, characteristic of coumarin. In $^1$H NMR, it showed three proton singlet at $\delta$ 2.31 due to CH$_3$ protons along with the peaks for other aromatic protons. Based on this data, the compound was identified as 4-methyl-3-phenylcoumarin (32) which was further confirmed by comparison of m.p. with literature value$^{48}$.

The present method for the preparation of 3-phenyl and 4-methyl-3-phenylcoumarins appears to be simple and efficient being one step process. Moreover, it is an eco-friendly procedure as it avoids the use of organic solvents at any stage of the reaction.
Following above procedure differently substituted 3-phenylcoumarins and 4-methyl-3-phenylcoumarins were prepared which are listed below:

(i) 3-phenylcoumarin

(ii) 6-methyl-3-phenylcoumarin
(iii)  7-methoxy-3-phenylcoumarin

(29)

(iv)  6-chloro-3-phenylcoumarin

(30)

(v)  6-bromo-3-phenylcoumarin

(31)

(vi)  4-methyl-3-phenylcoumarin

(32)
(vii) 6-bromo-4-methyl-3-phenylcoumarin

(viii) 4,6-dimethyl-3-phenylcoumarin

(ix) 7-methoxy-4-methyl-3-phenylcoumarin
**Experimental**

**Phenylacetyl chloride (26)**

A solution of phenylacetic acid (10 g) in thionyl chloride (15 ml) was refluxed in a round bottom flask fitted with a water condenser carrying a calcium chloride guard tube on a water bath for one hr until the evolution of SO₂ and HCl gases almost ceased. Excess of thionyl chloride was distilled off from the reaction mixture under reduced pressure and the residue was further distilled at reduced pressure to give phenylacetyl chloride as colourless liquid (26; 7.0 ml), b.p. 210°C (lit. 45 b.p. 210°C).

**3-Phenylcoumarin (27)**

A mixture of salicylaldehyde (0.60 ml), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle. The progress of the reaction was monitored by TLC and salicylaldehyde was found to have reacted almost completely after 5 min the reaction mixture was left at room temperature for another 5 min for completion of reaction. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 3-phenylcoumarin (27; 0.92 g), m.p. 138-39°C (lit. 30 m.p. 141°C).

IR (KBr): 1713 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 7.13-7.71 (m, 9H, Ar-H), 7.80 (s, 1H, H-4).

**6-Methyl-3-phenylcoumarin (28)**

A mixture of 2-hydroxy-5-methylbenzaldehyde (0.68 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 8 min and the completion of reaction was checked by TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 6-methyl-3-phenylcoumarin (28; 1.02 g), m.p. 142-44°C (lit. 46 m.p. 145°C).
IR (KBr): 1720 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.28 (s, 3H, CH\(_3\)), 7.25-7.70 (m, 8H, Ar-H), 7.76 (s, 1H, H-4).

**7-Methoxy-3-phenylcoumarin (29)**

A mixture of 2-hydroxy-4-methoxybenzaldehyde (0.76 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 7 min and the completion of reaction was checked on TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 6-methoxy-3-phenylcoumarin (29; 1.10 g), m.p. 129-30°C (lit.\(^{47}\) m.p. 126°C).

IR (KBr): 1720 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.80 (s, 3H, OCH\(_3\)), 7.23-7.71 (m, 8H, Ar-H), 7.76 (s, 1H, H-4).

**6-Chloro-3-phenylcoumarin (30)**

A mixture of 5-chloro-2-hydroxybenzaldehyde (0.78 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 9 min and the completion of reaction was checked on TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 6-chloro-3-phenylcoumarin (30; 1.19 g), m.p. 193-94°C (lit.\(^{43}\) m.p. 194°C).

IR (KBr): 1720 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.34-7.72 (m, 8H, Ar-H), 8.01 (s, 1H, H-4).

**6-Bromo-3-phenylcoumarin (31)**

A mixture of 5-bromo-2-hydroxybenzaldehyde (1.00 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 6 min and the completion of reaction was checked on TLC. The reaction
mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered washed with water and crystallized from ethanol to afford 6-bromo-3-phenylcoumarin (31; 1.32 g), m.p. 186-87°C (lit. 187-88°C).

IR (KBr): 1720 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 7.25-7.68 (m, 8H, Ar-H), 7.72 (s, 1H, H-4).

4-Methyl-3-phenylcoumarin (32)

A mixture of 2-hydroxyacetophenone (0.60 ml), phenylacetyl chloride (26; 0.70 ml) and potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle. The progress of the reaction was by TLC and 2-hydroxyacetophenone was found to have reacted almost completely after 5 min. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 4-methyl-3-phenylcoumarin (32; 0.96 g), m.p. 155-56°C (lit. 156°C).

IR (KBr): 1713 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 2.31 (s, 3H, CH₃), 7.25-7.69 (m, 9H, Ar-H).

6-Bromo-4-methyl-3-phenylcoumarin (33)

A mixture of 2-hydroxy-5-bromoacetophenone (1.10 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 9 min and the completion of reaction was checked on TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 6-bromo-4-methyl-3-phenylcoumarin (33; 1.30 g), m.p. 187-88°C (lit. 189°C).

IR (KBr): 1720 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 2.29 (s, 3H, CH₃), 7.25-7.79 (m, 8H, Ar-H).
4,6-Dimethyl-3-phenylcoumarin (34)

A mixture of 2-hydroxy-5-methylacetophenone (p-65; 0.75 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 6 min and the completion of reaction was checked on TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 4,6-dimethyl-3-phenylcoumarin (33; 1.10 g), m.p. 163-64°C (lit. 165°C).

IR (KBr): 1713 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 2.39 (s, 3H, 4-CH₃), 2.45 (s, 3H, 6-CH₃), 7.23-7.81 (m, 8H, Ar-H).

7-Methoxy-4-methyl-3-phenylcoumarin (35)

A mixture of 2-hydroxy-4-methoxyacetophenone (p-66; 0.83 g), phenylacetyl chloride (26; 0.70 ml), potassium carbonate (1.40 g) and 5 drops of water was ground in mortar with a pestle for 8 min and the completion of reaction was checked on TLC. The reaction mixture was acidified with conc. HCl after diluting it with ice cold water and the colourless solid thus obtained was filtered, washed with water and crystallized from ethanol to afford 7-methoxy-4-methyl-3-phenylcoumarin (35; 1.10 g), m.p. 105-06°C (lit. 108°C).

IR (KBr): 1713 cm⁻¹ (C=O).

¹H NMR (CDCl₃): δ 2.30 (s, 3H, CH₃), 3.90 (s, 3H, OCH₃), 6.90 (s, 1H, H-8), 7.30-7.60 (m, 7H, Ar-H).
References


